repeated and the residue of physiologically active peptide A was assayed. The results are shown in Table 8.

TABLE 8

	Residue of physiologically active peptide A (%)						
	Day 1	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8
Experimental Example 11	82.8	21.8	—	—	—	—	—
Experimental Example 12	96.7	91.7	79.5	69.2	59.2	—	22.8
Experimental Example 13	100.0	84.3	43.9	31.9	—	—	—
Experimental Example 14	96.3	67.5	38.0	23.5	—	—	—

(—: not determined)

Table 9 shows the linear regression models, correlation coefficients, and release periods as X-intercept which were determined from the data in Table 8 by the same procedures as used in Table 2.

TABLE 9

	Linear regression model	Correlation coefficient	Release periods (weeks)
Experimental Example 11	Residue (%) = 97.1−(75.7 × no. of weeks)	(R^2 = 0.994)	1.3
Experimental Example 12	Residue (%) = 92.2−(9.7 × no. of weeks)	(R^2 = 0.998)	10.3
Experimental Example 13	Residue (%) = 102.4−(24.8 × no. of weeks)	(R^2 = 0.982)	4.1
Experimental Example 14	Residue (%) = 97.7−(26.5 × no. of weeks)	R^2 = 0.989)	3.7

It is apparent from Tables 8 and 9 that the sustained-release preparation according to the present invention invariably insure a substantially constant release of the peptide over various segments of the time.

Comparative Example 1

400 mg of physiologically active peptide A acetate was added to a solution of a lactic acid-glycolic acid copolymer ((lactic acid/glycolic acid=50/50 (mole %), GPC weight average mol. wt.=58,000, GPC number average mol. wt.=14,000, number average mol. wt. by end-group determination=45,000; manufacturer; Boehringer-Ingelheim (Lot. RG505-05077), 3.6 g, in 33.2 g (25.0-ml) of dichloromethane but the physiologically active peptide A acetate could not be successfully dissolved.

Comparative Example 2

400 mg of physiologically active peptide A acetate was added to a solution of lactic acid-glycolic acid copolymer (lactic acid/glycolic acid=75/25 (mole %), GPC weight average mol. wt.=18,000, GPC number average mol. wt.=8,400, number average mol. wt. by end-group determination=30,000; manufacturer; Boehringer-Ingelheim (Lot. RG752-15057), 3.6 g, in 8.0 g (6.0 ml) of dichloromethane but the physiologically active peptide A could not be successfully dissolved. This dispersion was cooled to 17° C. and poured into 1,000 ml of a 0.1% aqueous solution of polyvinyl alcohol previously adjusted to 15° C. to prepare microcapsules in the same manner as in Example 11. The particle size distribution and physiologically active peptide A content of the microcapsules were 10 to 90 μm and 2.5% (w/w), respectively.

Comparative Example 3

400 mg of physiologically active peptide A acetate, was added to a solution of lactic acid-glycolic acid copolymer (lactic acid/glycolic acid=75/25 (mole %), GPC weight average mol. wt.=58,000, GPC number average mol. wt.=15,000, number average mol. wt. by end-group determination=53,000; manufacturer; Boehringer-Ingelheim (Lot. RG755-05019), 3.6 g, in 21.2 g (16.0 ml) of dichloromethane but the physiologically active peptide A could not be successfully dissolved. This dispersion was cooled to 17° C. and poured into 1,000 ml of a 0.1% aqueous solution of polyvinyl alcohol previously adjusted to 16° C. to prepare microcapsules in the same manner as in Example 11. The particle size distribution and physiologically active peptide A content of the microcapsules were 10 to 90 μm and 3.6% (w/w), respectively.

As shown in Comparative Examples 1 to 3, with a lactic acid-glycolic acid copolymer having substantially no terminal carboxyl group, the peptide [I] of the present invention could not be successfully dissolved.

Comparative Example 4

Leuprorelin acetate (manufacturer: Takeda Chemical Industries), 400 mg, was added to a solution of the same lactic acid-glycolic acid copolymer as used in Comparative Example 2, 3.6 g, in 8.0 g (6.0 ml) of dichloromethane but the leuprorelin acetate could not be successfully dissolved.

The sustained-release preparation of the present invention shows a constant release of the drug, especially the peptide [I] over a long time, thus being conducive to a lasting and stable effect. Furthermore, the duration of release of the drug can be easily controlled and excessive release immediately following administration can be inhibited. Specifically the histamine-releasing activity in the peptide [I] following administration of the sustained-release preparation is inhibited. The sustained-release preparation has excellent dispersibility. Moreover, the preparation is stable (e.g. to light, heat, humidity, colouring) and of low toxicity and, therefore, can be safely administered.

In accordance with the production method of the present invention, a sustained-release preparation containing a physiologically active peptide can be easily obtained in good yield. The thus obtained sustained-release preparation has a smooth surface and is excellent in mobility.

What is claimed is:

1. A method of producing a plurality of microcapsules together constituting a sustained-release preparation of leuprorelin which comprises:

(a) dissolving or suspending leuprorelin in an organic solvent solution comprising an organic solvent selected from the group consisting of halogenated hydrocarbons, alkyl ethers having three or more carbon atoms, alkyl esters of carboxylic acids wherein the alkyl group has four or more carbon atoms, aromatic hydrocarbons and mixtures thereof and a biodegradable polymer comprising a copolymer of lactic acid and glycolic acid to form a mixture;

(b) adding the mixture to an aqueous medium to provide an O/W emulsion; and

(c) transforming the mixture into microcapsules by removal of the organic solvent.